

TRANSMITTAL LETTER
(General - Patent Pending)

Docket No.
 14438

In Re Application Of: Michael J. McGehee, et al.

OCT 15 2001

Serial No.

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Filing Date

Examiner

Group Art Unit

Title: CONOTOXIN PEPTIDES

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

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**Protest Under 37 C.F.R. 1.291(a)
11 (eleven) references**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#9

In re Application of:

Michael J. McIntosh
Baldomero Olivera
Lourdes Cruz

Attn: Office of Petitions
Crystal Park 1, Room 520

Serial No: Unknown

Filed: Between January 29, 2000
and December 28, 2000

Priority: U.S. Provisional Patent
Application Serial No.
60/118,381, filed 1/29/99;
60/173,343, filed 12/28/99

Related to: International Application
Number PCT/US00/01978

Filed: January 28, 2000

For: CONOTOXIN PEPTIDES

Assignee: University of Utah
Research Foundation,
Salt Lake City, UT 84108

Assistant Commissioner for Patents
Washington, D.C. 20231

PROTEST UNDER 37 C.F.R. §1.291(a)

Sir:

The protestor, through the undersigned respectfully requests that the materials enclosed herewith be considered during examination of the above-identified patent application ("the McIntosh U.S. application").

1. Sawynok, J. et al., (August 1999) Pain 82(2): 149-158 (hereinafter "Sawynok, et al.")
2. Ardid, D. et al., (1992) Fund. Clin. Pharmacology 6(2): 75-82 (hereinafter "Ardid, et al.")

3. Kawamata, et al., (September 1999) Br. J. Anaesth 83(3): 449-452 (hereinafter "Kawamata, et al.")
4. Reimann, et al., (January 1999) Anesth Analg 88(1): 141-145 (hereinafter "Reimann, et al.")
5. Yaksh, T.L. (1985) Pharmacology Biochemistry & Behavior 22: 845-858 (hereinafter "Yaksh I")
6. Yaksh T.L. & Takano, Y. (1992) J. Pharmacology & Experimental Therapeutics 261(2): 764-772 (hereinafter "Yaksh II")
7. Yaksh, T.L. & Howe, J.R. (1982) J. Pharmacology & Experimental Therapeutics 220(2): 311-321 (hereinafter "Yaksh III")
8. Howe, J.R., et al. (1983) J. Pharmacology & Experimental Therapeutics 224(3): 552-558 (hereinafter "Howe, et al.")
9. Solomon, et al., (1989) J. Pharmacology & Experimental Therapeutics 251(1): 28-38 (hereinafter "Solomon, et al.")
10. Fleetwood-Walker, S.M. et al., (1985) Brain Research 334: 243-254 (hereinafter "Fleetwood-Walker, et al.")
11. International Application WO 00/20444, published April 13, 2000 (hereinafter "International Application WO 00/20444")

I. DISCUSSION OF THE CITED REFERENCES

The protestor has not reviewed the claims in the University of Utah U.S. applications¹ and requests that all pending claims in each application be examined in view of these references. To the extent that the pending claims in the University of Utah U.S. non-provisional application(s) are similar to the claims in the University of Utah PCT applications, these references may, either alone or in combination, render one or more of the pending claims unpatentable. To facilitate review of these references, the following sections highlight passages that may be of particular relevance.

¹ Protestor believes that one or both of the University of Utah Provisional Applications 60/118,381 filed January 29, 1999 and/or 60/173,343 (apparently, 60/173,198) were converted to U.S. non-provisional applications by December 28, 2000.

1. Sawynok, et al.

Sawynok, et al. disclose that amitriptyline, a non-selective noradrenaline (NA) and 5-hydroxytryptamine a (5-HT) reuptake inhibitor, produce a peripheral antinociceptive action in an inflammatory (formalin test) and a neuropathic pain model (spinal nerve ligation). Sawynok, et al. assessed whether desipramine, a selective NA reuptake inhibitor, and fluoxetine, a selective 5-HT reuptake inhibitor, could produce peripheral antinociceptive actions in these same tests. Effects on paw volume also were assessed. In the 2.5% formalin test, desipramine and fluxetine 10-300 nmol produced a dose-related reduction in phase 2 (16-60 min) flinching and biting/licking behaviors when coadministered with the formalin. Phase 1 flinch behaviours (0-12 min) were significantly reduced at the highest dose. These actions are peripherally mediated, as they were not seen when desipramine or fluoxetine (100, 300 nmol) were injected into the contralateral hindpaw. The peripheral action of desipramine and fluoxetine was not altered by coadministration of caffeine 1500 nmol. In the spinal nerve ligation model, desipramine 100 nmol, but not fluoxetine 100 nmol, produced a peripheral antihyperalgesic action in the hindpaw corresponding to the ligated side when thresholds were determined using a thermal paw stimulator.

In paw volume experiments, desipramine, at doses which are maximally effective in behavioral tests, produced only a slight increase in paw volume, but fluoxetine (10-300 nmol) produced a robust and sustained dose-related increase in paw volume. Amitriptyline also produced minimal effects on paw volume. When coinjected with formalin, no agent significantly altered the degree of paw swelling produced by formalin. The increase in paw volume produced by fluoxetine was inhibited by ketanserin (5-HT₂ receptor antagonist),

mepyramine (histamine H1 receptor antagonist) and phentolamine (alpha-adrenergic receptor antagonist), but not by the other selective 5-HT receptor antagonists tested or caffeine.

The pronounced peripheral pain alleviating actions in the absence of marked changes in paw volume produced by desipramine and amitriptyline, but not fluoxetine, in the formalin test and the spinal nerve ligation model suggest that these agents could be developed as cream or gel formulations to recruit a peripheral antinociceptive action in inflammatory and neuropathic pain states. Such a formulation could permit the attainment of higher and more efficacious concentrations in the region of the sensory nerve terminal, with limited systemic side effects.

2. Ardid, et al.

Ardid, et al. compared the analgesic effect of acute injections (1.25 and 20 mg/kg, ip) of several antidepressants with different effects on monoamine reuptake, on two pain tests in mice (hot-plate and phenylbenzoquinone-induced abdominal writhes). Serotonergic inhibitors (citalopram, fluvoxamine and clomipramine) were more effective in the writhing test. The mixed antidepressants (amitriptyline and to a lesser degree trimipramine) were more effective in the two tests than the other antidepressant drugs. Changes in motor activity of clomipramine and amitriptyline could not account for the modifications of pain threshold. Amineptine (a dopamine reuptake inhibitor) failed to induce any antinociceptive affect in the hot-plate test and was hyperalgesic in the writhing test, which could be explained by an increased motor activity. The Ardid, et al. findings indicate that the antinociceptive potency of reuptake inhibitors varies according to their monoamine specificity and the nature of stimuli. These results suggest that the preferential choice of serotonergic antidepressants in the management of chronic pain is arguable.

3. Kawamata, et al.

Kawamata, et al. examined if intathecal desipramine, a selective norepinephrine reuptake inhibitor, would modulate peripheral inflammation-induced hyperalgesia. Rats were chronically implanted with a lumbar intrathecal catheter and paw withdrawal latency (PWL) to noxious heat stimuli was assessed. Unilateral hindpaw inflammation was induced by intraplantar carrageenan injection. Carrageenan injection significantly reduced PWL of the injected paw, but not of the contralateral side. Intrathecal desipramine (10, 30, 60 and 100 micrograms), which did not produce analgesic effects in untreated rats, dose-dependently reversed the shortened PWL on the ipsilateral side without affecting the contralateral side. Pretreatment with intrathecal yohimbine (10 micrograms) did not antagonize the anti-hyperalgesic effects of desipramine. The results of Kawamata, et al. suggest that the mechanism underlying the analgesic effect of desipramine on inflammation-induced hyperalgesia is unlikely to be inhibition of norepinephrine reuptake within the spinal cord.

4. Reimann, et al.

Reimann, et al. disclose that antinociception can be produced at the spinal level by activation of opioidergic, noradrenergic, and serotonergic systems. Reimann, et al. tested the antinociceptive effects of combined activation of all three systems. Antinociception was assessed in the rat tail flick test, and drugs were administered via an intrathecal catheter. Morphine, desipramine, and serotonin produced antinociception of their own. The combination of subthreshold doses of morphine 1 µg and of desipramine 3 µg produced pronounced antinociception that was antagonized by yohimbine. The combination of subthreshold morphine with serotonin 50 µg or desipramine with serotonin caused only small antinociceptive effects.

When morphine combined with desipramine was decreased to a subthreshold dose, Reimann, et al. observed pronounced antinociception when a subthreshold dose of serotonin was added. Reimann, et al. further disclose that the activation of all three neurotransmitter systems with small doses of agonists may represent an effective principle for pain control at the spinal level.

5. Yaksh I

Yaksh I teaches that spinal alpha₂ receptor agonists produce a powerful analgesic effect in mouse, rat, cat, primate and man. The following excerpts may be of particular relevance to claims corresponding to Claims 16-20 of the University of Utah PCT application.

“In the rat, intrathecal administration of adrenergic agonists produces a dose dependent increase in the response latency or the hot plate and tail flick” (page 848, right column, 2nd full paragraph).

“These data offer clear support for the concept that in all species tested, including man, the spinal action of alpha agonists produces a powerful analgesia” (page 848, left column, lines 24-27).

“...the spinal effects of alpha₂ agonists on pain evoked behavior is preferentially antagonized by agents with a relative selectivity for the alpha₂ receptor” (page 850, right column, lines 3-6).

6. Yaksh II

Yaksh II teaches that subclasses of alpha-2 adrenergic receptors are capable of inducing an analgesic effect. The following excerpts may also be of particular relevance to claims corresponding to Claims 16-20 of the University of Utah PCT application.

“...we have systemically examined the potency of competitive antagonists in reversing the antinociceptive effects of three i.t. administered alpha-2 agonists... These observations suggest that clonidine (CLON) and dexmedetomidine (DMET) act upon sites which are essentially indistinguishable, but different from the site acted upon in the spinal cord by ST-91. For both pharmacological and functional reasons, we believe the ST-91 site to be a subclass of the alpha-2 receptor” (page 770, right column, lines 53-62).

7. Yaksh III

Yaksh III discloses that the relationship between inhibition of neuronal amine transport and the treatment of pain was well known prior to the priority date of the University of Utah application.

“Intrathecal pretreatment with 5,6-DHT or 6-OHDA elicited hyperalgesia, as evidenced by a significant decrease in thermal nociceptive threshold” (page 319, right column, lines 56-58).

8. Howe, et al.

The following excerpts of Howe, et al. may be of particular relevance:

“Our results suggest that stimulation of either one of two separate populations of postsynaptic spinal alpha adrenoceptors will inhibit spinal nociceptive transmission” (Abstract)

“In summary, we think our results indicate that activation of either one of two separate populations of spinal alpha adrenoreceptors can produce analgesia” (pages 557-558, right column, lines 62-62).

9. Solomon, et al.

Solomon, et al. teach, inter alia, that a specific alpha adrenoceptor agonist, clonidine, produces analgesic properties in rats and in humans when administered intrathecally. The following excerpts may have particular relevance to claims corresponding to Claims 16, 17 and 20.

“Clonidine (3.2-32.0 µg i.t.) produced inhibition of the nociceptive tail flick reflex in rats... the results suggest that between 1.0µg and 3.2 µg [would be the effective dose] (page 33, right column, lines 32-38).

10. Fleetwood-Walker, et al.

The following excerpts of Fleetwood-Walker, et al. may be of particular relevance:

“A characteristic feature of neurones in the dorsal horn of the lumbar spinal cord, that respond to cutaneous sensory stimuli is that they are subject to powerful supraspinal modulation” (page 243, right column, lines 1-4).

“Intrathecal application of drugs has been used to investigate a potent spinal effect of L-noradrenalin in producing behavioral changes suggestive of analgesia. In rats and in primates, alpha 2 but not alpha 1, or beta agonists produced behavior consistent with selective inhibitors of both propriospinal and supraspinal reflexes to noxious stimulation...” (page 252, right column, lines 40-43).

11. International Application WO 00/20444

International Application WO 00/20444 teaches isolated, synthetic or recombinant χ -conotoxin peptides capable of inhibiting neuronal amine transport and nucleic acids encoding all or part of the peptides; antibodies to the peptides; and methods of treating urinary or cardiovascular conditions or diseases, mood disorders, pain or inflammation.

International Application WO 00/20444 provides χ -conotoxin peptides including SEQ ID NO: 1 (identified as χ -MrIA on p. 3) which corresponds to the sequence MAR 1 (page 8, lines 26-27) of the University of Utah application. The disorders purportedly treatable with the MAR1 conotoxin peptide of the University of Utah include cardiovascular disorders, mood disorders and urinary incontinence. (See 60/118,381 filed January 28, 1999, page 2, lines 12-18).

II. CONCLUSION

The Protestor has not reviewed the claims of the University of Utah U.S. application(s) and requests that the Examiner compare all pending claims with the references described above. To the extent that the claims in the University of Utah U.S. application(s) are similar to the claims in the University of Utah PCT application, these references, either alone or in combination, may render one or more pending claims unpatentable.

Additionally, the Protestor hereby certifies that a duplicate copy of this Protest and all cited references has been sent to Jeffery L. Ihnen, Esq., the agent of record named in the PCT application by first class mail on October 11, 2001, at the following address:

Rothwell, Figg, Ernst & Kurz
Suite 701 East, 555 13th Street N.W.
Columbia Square, Washington, DC 20004

Dated: October 11, 2001

Respectfully submitted,

Scully, Scott, Murphy & Presser



Frank S. DiGilio
Registration No. 31,346

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true copy of this PROTEST UNDER
37 C.F.R. §1.291(a) will be served via first class mail addressed to the party as follows:

Rothwell, Figg, Ernst & Kurz
Suite 701 East, 555 13th Street N.W.
Columbia Square, Washington, DC 20004

Dated: October 11, 2001



Peter I. Bernstein